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Bilateral isolated sixth cranial nerve palsy after unilateral intravitreal Ranibizumab injection: Case report and review of literature

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Abstract

Ranibizumab is an anti-vascular endothelial growth factor agent that has revolutionized the treatment of diabetic macular edema. Although the systemic safety profile of ranibizumab is generally favorable, it could rarely cause adverse effect such as microvascular cranial nerve palsy. A 68-year-old man who has right centrally-involved diabetic macular edema presented with binocular diplopia and squint five days after his first dose of intravitreal ranibizumab injection. His pupils were equal and reactive to light with no relative afferent pupillary defect. Hirschberg test revealed bilateral esotropia at primary gaze, while ocular motility exam showed bilateral abduction deficit. Bilateral lateral rectus palsy was further confirmed with Hess test. Other neurological examination was negative. Given the recent intravitreal ranibizumab injection, the bilateral sixth cranial nerve palsy was attributed to ranibizumab injection causing microvascular complication. The lateral rectus function improved at 3-month follow up. This is the first case report of bilateral sixth cranial nerve palsy that developed following intravitreal ranibizumab injection. We propose that the unilateral intravitreal ranibizumab injection has triggered a systemic microvascular disturbance, resulting in bilateral abducens nerve ischemia.

Keywords: Anti-VEGF, ranibizumab, diabetic macular edema, bilateral sixth cranial nerve palsy, intravitreal injection

INTRODUCTION

Ranibizumab is an anti-vascular endothelial growth factor (VEGF) agent that has revolutionized the treatment of diabetic macular edema, neovascular age-related macular degeneration, and retinal vein occlusions.[1] It binds to human VEGF-A protein that plays an important role in promoting increased vascular permeability, thus inhibiting angiogenic activity.[1]

Clinically we understand that VEGF suppression via systemic administration is associated with cardiovascular and arterial thromboembolic adverse events.[1] While multiple recent meta-analysis suggested that the systemic safety profile of ranibizumab is generally favorable, this may not be applicable to the real-world as many studies excluded patients with pre-existing systemic vascular conditions.[2] Therefore, reporting of the systemic adverse effects of ranibizumab is pivotal as most of our real-world patients who require frequent intravitreal ranibizumab injections are the elderly, who are at increased risk for cerebrovascular and cardiovascular events.

In this report, we describe a case of microvascular bilateral sixth cranial nerve palsy after intravitreal Ranibizumab injection and describe the possible pathophysiology behind this rare systemic complication.

CASE REPORT

A 68-year-old man who has underlying type two diabetes mellitus was under our follow up for bilateral eye moderate non-proliferative diabetic retinopathy with right eye diabetic macular edema. He is a non-smoker and has no history of cardiovascular disease, renal impairment, or stroke. He received the first dose of intravitreal ranibizumab (0.3mg/0.03ml) over his right eye.

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However, five days after injection, he presented to us with binocular diplopia at both primary and lateral gazes. His wife also noticed that both of his pupils appeared to be "moving towards his nose". He denied of any recent head trauma, amaurosis fugax or upper and lower limb weakness.

His best corrected visual acuity was 6/36 over the right eye, and 6/20 over the left eye. His pupils were equal and reactive to light with no relative afferent pupillary defect. Intraocular pressure and anterior segment examination of both eyes were normal, except for nuclear sclerosis cataract in both eyes. The fundus examination of both eyes showed pink optic disc, not swollen, and moderate non-proliferative diabetic retinopathy changes with dull fovea. Hirschberg test revealed 15 prism dioptres esotropia over both eyes at primary gaze. Ocular motility exam showed a marked abduction deficit of -1 over his right eye and -3 over his left eye (Figure 1A), and bilateral lateral rectus palsy was further confirmed with Hess test (Figure 2A). Confrontation test was normal for both eyes. The other cranial nerves and neurological examinations were also normal.

His blood pressure on presentation was 145/80mmHg and blood glucose was 4.6mmol/L. Full blood count, renal profile, erythrocyte sedimentation rate, thyroid function test were also normal. His blood haemoglobin $A1_C$ was 6.4%. CT brain showed no evidence of recent infarct or haemorrhage.

Our impression was bilateral isolated sixth cranial nerve palsy secondary to microvascular ischemia, related to intravitreal ranibizumab injection in view of the development of diplopia within a week after his first dose of injection. He was referred to medical team for optimization of his premorbid and commencement of aspirin.

At 3 months follow up, his best-corrected visual acuity has improved to 6/24 over the right eye and 6/12 over the left eye. The grade of his abduction limitation showed significant improvement (Figure 1B), and his Hess test showed marked improvement in terms of lateral rectus function (Figure 2B).

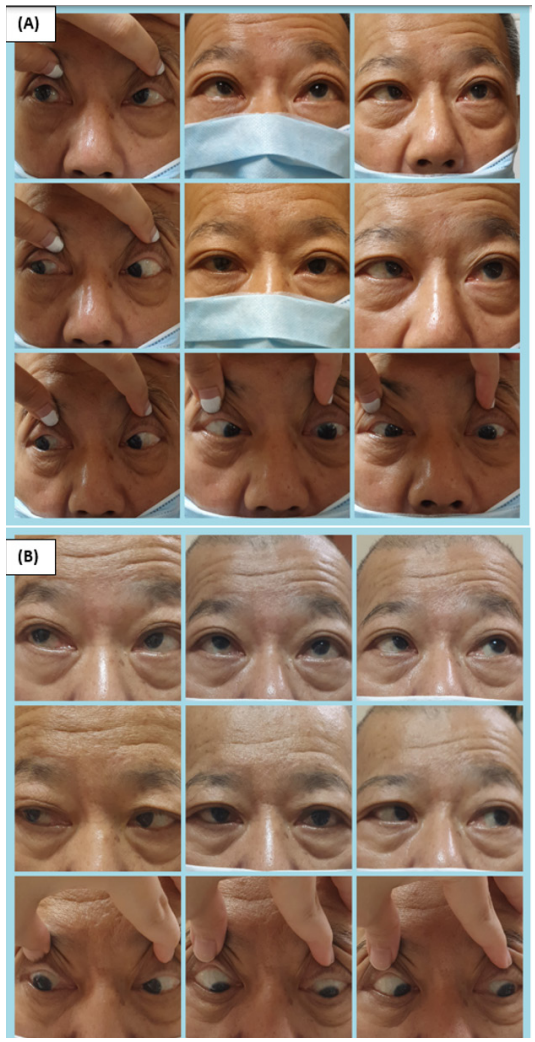

Figure 1. Eye movements at 9 gazes (superotemporal, superior, superonasal, temporal, primary, nasal, inferotemporal, inferior, inferonasal) at (A) day 5 of diplopia and (B) 3 months of diplopia

DISCUSSION

VEGF is not only essential in regulating vascular angiogenesis, dilatation and permeability[1], but also helps in restoring homeostasis after ischemia-reperfusion conditions.[3] In diabetic macular edema, there is increased expression of intraocular VEGF leading to blood retinal barrier breakdown, neovascularization, haemorrhages, microaneurysms, and retinal vascular leakage. Ranibizumab has revolutionized the treatment of DME by binding to VEGF-A isoforms to reduce intraocular VEGF level. However, clinical experiences in oncology remind us that reduced serum VEGF levels are associated with cardiovascular, arterial thromboembolic, renal and gastrointestinal adverse events.[1,3]

Ranibizumab is a monoclonal antibody-antigen binding fragment (Fab) engineered specifically to inhibit all biological VEGF-A isoforms. It has a small molecular size and lack of Fc antibody region, thus allowing it to be cleared from systemic circulation rapidly. Vitreous elimination half-life of ranibizumab is estimated to be 9

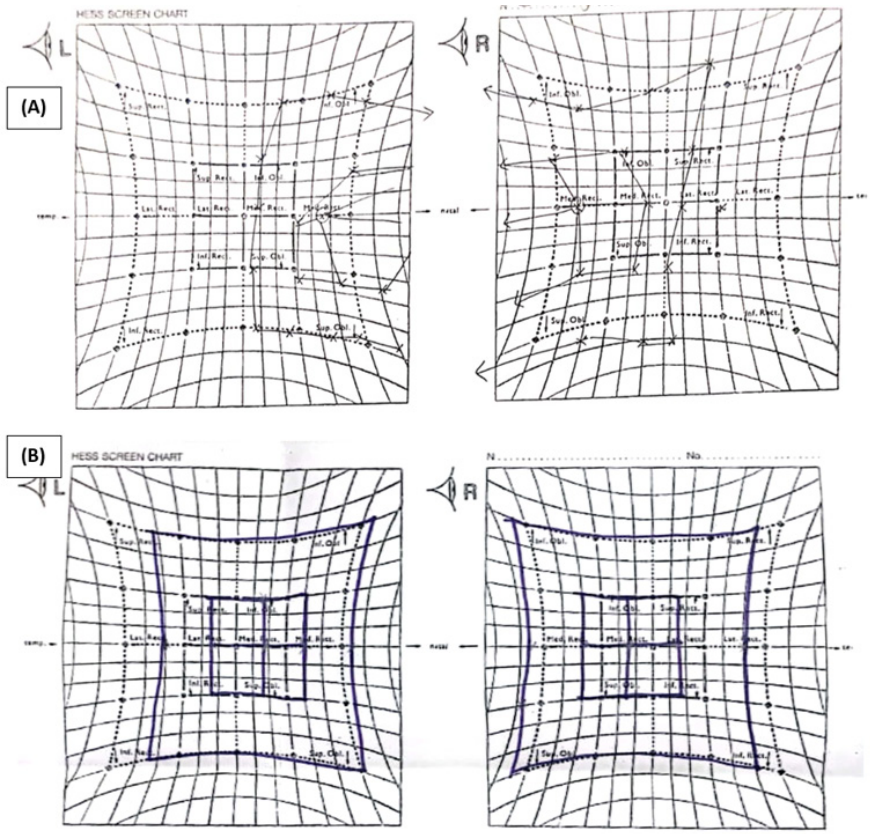

Figure 2. Hess test at (A) day 5 of diplopia showing bilateral lateral rectus restriction and (B) at 3 months of diplopia showing significant improvement in lateral rectus function

days, while the systemic elimination half-life of that is approximately 2 hours[1,4], making its systemic-to-vitreous exposure ratio to be very low. However, because the ranibizumab deposited in the stagnant vitreous exiting slowly into the systemic circulation, the evident serum half-life following intravitreal injection was 9 days[4], suggesting possibility of systemic adverse effect.

Sugimoto *et al*. demonstrated a prominent increment of plasma monocyte chemoattractant protein-1 (MCP-1) level post-intravitreal ranibizumab injection.[3] MCP-1 is known to play a key role in atherosclerosis formation, and it reflects the development of inflammatory response in heart and brain in the presence of both permanent and transient focal ischemia.[5] The plasma level of MCP-1 is independent of common risk factors such as diabetes and hypertension.[5] This implies that intravitreal ranibizumab injection is linked to development of myocardial and cerebral ischemia despite its short systemic half-life.

VEGF plays a vital role in maintaining microvascular integrity, and its inhibition has been shown to induce arteriolar vasoconstriction lasting up to a year, regardless of injection frequency.[6] Although rare, there is possibility of systemic absorption from intravitreal ranibizumab resulting in vascular effect. We propose that in this case, systemic effect of ranibizumab triggered microvascular disturbance, resulting in bilateral abducens nerve ischemia through vasospasm or impaired perfusion.

In this case, although our patient's bilateral isolated sixth cranial nerve palsy can be attributed to diabetes, but his sugar control was excellent, and the nerve palsy developed within a week after intravitreal ranibizumab injection. Therefore, we postulate that his microvascular bilateral sixth nerve palsy is likely attributed to systemic effect from intravitreal ranibizumab injection given the temporal proximity.

Furthermore, patients with isolated sixth cranial nerve palsy are 5.8 times more likely to develop stroke as compared to sociodemographically-matched peers, and this risk remains elevated for the next five years.[7] In our case, we referred our patient to medical team promptly for optimization of his premorbid and commencement of aspirin

Table 1: Literature review of reported cases of cranial nerve palsies following intravitreal anti-VEGF injection

Author/ year	Type of anti-VEGF	Comorbid	Indication	Cranial nerve palsy	Days after last injection	Outcome
Caglar *et al.*[9], 2015	Ranibizumab	Diabetes mellitus	DME	Right 6th nerve palsy	4 days after 2nd injection	Resolution at 100th day
Cakmak *et al.*[8], 2010	Bevacizumab	Diabetes mellitus	AMD	Right 6th nerve palsy	7 days after 1st injection	Resolution at 3 months
Micieli *et al.*[10], 2009	Ranibizumab	Hypertension	AMD	Right 3rd nerve palsy	16 days after 13th injection	Resolution at 53rd day

and terminated his subsequent intravitreal ranibizumab injections to prevent him from developing stroke.

Till date, there has been only two cases of unilateral isolated sixth cranial nerve palsy following intravitreal bevacizumab[8] and ranibizumab[9] injections reported, which developed within a week after intravitreal ranibizumab injection. There is also a reported case of unilateral third cranial nerve palsy following intravitreal ranibizumab injection.[10] All three cases achieved resolution at 3 months (Table 1). To the best of our knowledge, this is the first case report that discuss bilateral sixth cranial nerve palsy that developed within a week following one dose of intravitreal ranibizumab injection.

This case illustrates a possible causal relationship of cranial nerve palsy with ranibizumab injection. Although intravitreal ranibizumab injections are generally well-tolerated, it is important to be mindful of the potential association between microvascular disturbances and intravitreal anti-VEGF injection. In the event of microvascular cranial nerve palsies post-intravitreal ranibizumab injection, subsequent injections should be withheld, and early co-management with medical team is crucial to prevent development of stroke in the future.

DISCLOSURE

Ethics: Informed consent has been obtained from the patient for this report.

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Conflicts of interest: None

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